Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 6, pp. 825–827, 1997

Printed in Great Britain
PII: S0957-4166(97)00060-8
0957-4166/97 $17.00 + 0.00

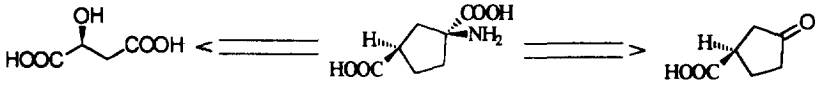
Stereospecific synthesis of (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid, a selective agonist of metabotropic glutamate receptors

Dawei Ma,* Jingyuan Ma and Lixin Dai

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Abstract: (1*S*,3*R*)-Aminocyclopentane-1,3-dicarboxylic acid **1**, a widely used metabotropic glutamate receptor agonist has been synthesized. Hydrolysis followed by Curtius rearrangement of **5** derived from dimethyl (*S*)-malate gave **6** with excellent diastereofacial selectivity (>97% de), which was converted into **1** through an S_N2 reaction of mesylate **7** with tetraethylammonium cyanide. © 1997 Elsevier Science Ltd. All rights reserved.

L-Glutamate, a major neurotransmitter in excitatory synaptic pathways of the mammalian central nervous system (CNS)[1], plays an important role in many integrative brain functions[1,2]. Glutamate receptors have been classified into two distinctive groups termed ionotropic and metabotropic receptors[1,2]. The ionotropic receptors consist of N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), and kainate receptors that contain glutamate-gated, cation-specific ion channels. The metabotropic glutamate receptors (mGluRs) are different both functionally and pharmacologically from ionotropic receptors. The mGluRs are coupled to G-proteins that mediate a variety of transduction mechanisms[3]. (1*S*,3*R*)-1-Aminocyclopentane-1,3-dicarboxylic acid (1*S*,3*R*)-ACPD, **1**, a conformationlly constrained analog of glutamate, was found to be a selective agonist for mGluRs and has played a crucial role in seeking the functions of *in situ* mGluRs[1–4]. Recently, some studies have shown that (1*S*,3*R*)-ACPD has potential value in treatment of some neurodegenerative disorders[4,5]. However, in comparison with its biological importance, little synthetic studies were undertaken. The previously reported synthesis[6] of **1** began with (*R*)-3-oxocyclopentanecarboxylic acid (Scheme 1). Chemical resolution is needed to get this acid. Moreover, Bucherer–Bergs reaction of (*R*)-3-oxocyclopentanecarboxylic acid gave a mixture of cis and trans isomers in 1:1 ratio and the desired product had to be isolated by fractional crystallization. In addition, this method is limited for the synthesis of other analogues of (1*S*,3*R*)-ACPD that are actively being pursued for evaluation of more potent and selective ligands for different subtypes of mGluR[7–10]. Herein we describe the first enantiospecific synthesis of (1*S*,3*R*)-ACPD.

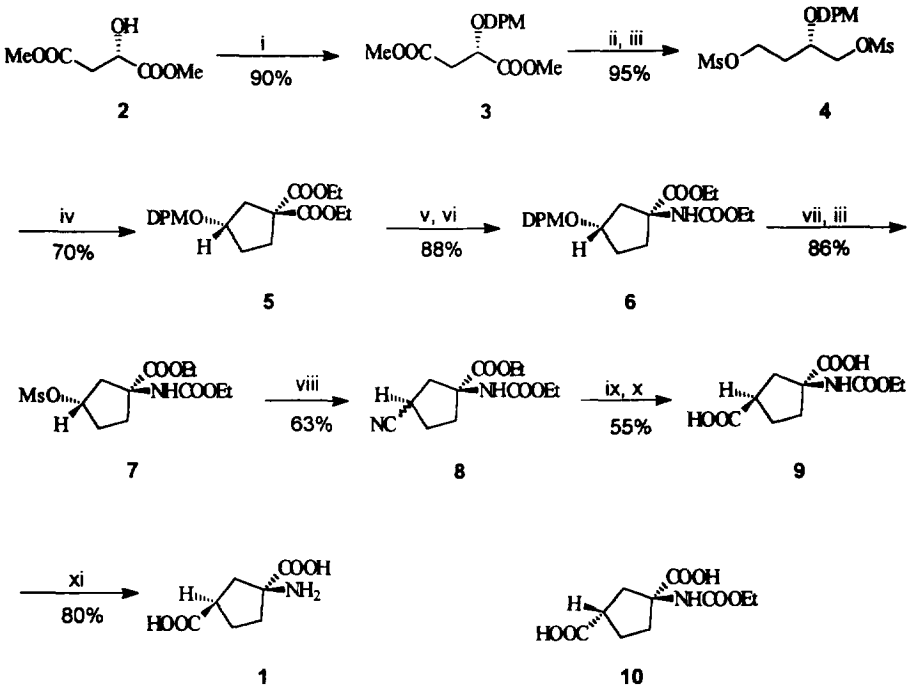


1

Scheme 1.

In designing a practical, asymmetric synthesis we chose dimethyl (*S*)-malate which can be obtained from L-malic acid as starting material. As outlined in Scheme 2, treatment of dimethyl (*S*)-malate with tri-diphenylmethyl phosphate under the catalytic effect of TFA produced **3** ($[\alpha]_D^{25}=-99.5$ (MeOH, c=1.1)) in 90% yield[11].

* Corresponding author. Email: madw@pub.sioc.ac.cn



Reagents and Conditions: i, $P(O)(ODPM)_3$, TFA, $CHCl_3$; ii, $LiAlH_4$, THF, 0 °C-25 °C; iii, MsCl, Et_3N, CH_2Cl_2; iv, $CH_2(COOEt)_2$, NaOEt, EtOH, reflux; v, NaOH, EtOH, H_2O, 0 °C-25 °C, 2 days; vi, $(PhO)_2P(O)N_3$, Et_3N, benzene, reflux, then EtOH; vii, H_2, Pd/C, 30 atm, EtOH; viii, Et_4NCN, MeCN, 40 °C; ix, HCl, EtOH, r.t.; x, LiOH, EtOH, H_2O, then HCl; xi, iodotrimethylsilane, CH_3CN, 40 °C, then propylene oxide, EtOH, reflux for 15 min.

Scheme 2.

The diester **3** was then reduced with LAH to the diol followed by mesylation of both hydroxy groups to afford **4** ($[\alpha]_D^{25}=-49.9$ (CH_3Cl, c=0.9)). The condensation of **4** with 1 equiv of diethyl malonate under the action of 2 equiv of NaOEt gave the cyclization product **5**. The ethyl ester trans to the DPMO group was selectively hydrolyzed with 1.2 equiv of sodium hydroxide to generate the monoacid. Without further purification, this monoacid was treated with DPPA to form the corresponding acid azide, which was converted into carbamate **6**[12] by means of a Curtius rearrangement[13]. At this time we could examine the enantioselectivity for hydrolysis reaction. By HPLC it was found that only 3% of the cis product existed in the crude product, which could be removed by column chromatography. Remarkably, we found that if a benzyl group was used as protecting group in this synthesis, the ratio of cis and trans was about 1:3. Next, the DPM group of **6** was removed by Pd-catalyzed hydrogenation and the resultant alcohol was converted to its mesylate **7** ($[\alpha]_D^{20}=-1.86$ (CH_3Cl, c=1.45)) in 86% yield. Attempts to transfer **7** to nitrile **8** by a S_N2 reaction proved quite troublesome. For example, reactions of **7** with sodium cyanide in many solvents such as dimethyl sulfide, acetonitrile and HMPA, and at different temperature proceeded in unsatisfactory yields (lower than 20%). After many attempts we found that Simchen's method[14] could give the desired product in moderate yield and diastereoselectivity. Heating a mixture of **7** with tetraethylammonium cyanide in acetonitrile at 40°C produced **8** in 63% yield. The ratio of (1*S*,3*R*)-**8** and (1*S*,3*S*)-**8** was 7:3 determined by ^1H NMR,

which implied that there had some S_N1 reaction occurred in this case. Since the two isomers were inseparable by column chromatography, they were directly used for next step. Thus, after treatment of **8** with gaseous HCl saturated ethanol at room temperature, the resulting diester was hydrolyzed with lithium hydroxide to give diacid **9** and its epimer **10**, at this stage we could separate two isomers by column chromatography and the pure isomer **9**[15] was obtained in 35% overall yield (from mesylate **7**). Finally, deprotection of **9** with iodotrimethylsilane in acetonitrile followed by quenching with water afforded (1*S*,3*R*)-ACPD salt[16], which was treated with propylene oxide to release **1** ($[\alpha]_D^{20}=-10.4$ (6N HCl, c=0.8)) in 80% yield. Its spectral properties are identical with that reported[6].

In conclusion, we have developed the first enantiospecific synthesis of (1*S*,3*R*)-ACPD. This synthetic method provided another example of synthesizing biologically important molecules by employing L-malic acid as starting material. The synthesis of designed analogues based on this synthetic protocol and their biological evaluation are currently underway.

Acknowledgements

Financial support from the Chinese Academy of Sciences, National Natural Science Foundation of China, the State Committee of Science and Technology of China is gratefully acknowledged.

References

1. Nakanishi, S. *Science* **1992**, *258*, 597.
2. Seeburg, P. H. *Trends Neurosci.* **1993**, *9*, 359.
3. Schoepp, D. D.; Conn, P. J. *Trends Pharmacol. Sci.* **1993**, *14*, 13.
4. For reviews, see Knopfel, T.; Kuhn, R.; Allgeier, H. *J. Med. Chem.* **1995**, *38*, 1417. Ornstein, P. L.; Schoepp, D. D.; Monn, J. A. *Current Pharmaceutical Design* **1995**, *1*, 355. Knopfel, T.; Gasparini, F. *Drug Discovery Today* **1996**, *1*, 103.
5. Eveleth, D. D.; Kelleher, J. A.; Cotman, C. W. *PCT Int. Appl.* WO 94 27,602, *Chem. Abst.* **1995**, *122*, 123164.
6. Curry, K.; Peet, M. J.; Magnuson, D. S. K; McLennan, H. *J. Med. Chem.* **1988**, *31*, 864.
7. Tellier, F.; Acher, F.; Brabet, I.; Pin, J.-P.; Bockaert, J.; Azerad, R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2627.
8. Schoepp, D. D.; Johnson, B. G.; Salhoff, C. R.; Valli, M. J.; Desai, M. A.; Burnett, J. P.; Mayne, N. G.; Monn, J. A. *Neuropharmacology* **1995**, *34*, 843.
9. Ezquerra, J.; Yruretagoyena, B.; Avendano, C.; Cuesta, E.; Gonzalez, R.; Prieto, L.; Pedregal, C.; Espada, M.; Prowse, W. *Tetrahedron* **1995**, *51*, 3271.
10. Larue, V.; Gharbi-Benarous, J.; Acher, F.; Valle, G.; Crisma, M.; Toniolo, C.; Azerad, R.; Girault, J.-P. *J. Chem. Soc. Perkin Trans 2* **1995**, 1111.
11. Lapatsanis, L. *Tetrahedron Lett.* **1978**, 4697.
12. Selected data for **6**: $[\alpha]_D^{25}=-4.18$ (CH_3Cl, c=1.45); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.19 (m, 10H), 5.40 (s, 1H), 4.95 (s, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 4.06 (q, *J*=7.1 Hz, 2H), 2.49–2.32 (m, 3H), 2.01–1.88 (m, 3H), 1.24 (t, *J*=7.1 Hz, 3H), 1.20 (t, *J*=7.1 Hz, 3H); MS m/z 326 (M^+-73), 278, 167; Anal. Calcd. for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10, N, 3.40; found: C, 69.89; H, 7.34; N, 3.60.
13. Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203.
14. Simchen, G.; Kobler, H. *Synthesis* **1975**, 605.
15. Selected data for **9**: $[\alpha]_D^{25}=-27.6$ (MeOH, c=0.7); ^1H NMR (300 MHz, $CDCl_3$) δ 4.10 (q, *J*=7.1 Hz, 2H), 3.18 (m, 1H), 2.57 (dd, *J*=14.5, 8.4 Hz, 1H), 2.39–1.95 (m, 5H), 1.17 (t, *J*=7.0 Hz, 3H).
16. Jung, M. E.; Lyster, M. A. *J. Chem. Soc. Chem. Commun.* **1978**, 315.

(Received in Japan 7 January 1997)